REMARKS/ARGUMENTS

Status of the Claims

Claims 1-3, 6-13, 15-19, 21 and 22 are pending with entry of this amendment. Claims 4, 5, 14, 20 and 23 to 65 being cancelled. Claims 1 and 6 to 8 are amended herein. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice to renewal of the claims in their original form and are not to be construed as abandonment or dedication of the previously claimed subject matter or agreement with any objection or rejection of record.

The amendments to claims 1, 7, and 8 merely add SEQ ID NOs as requested by the Examiner, and therefore introduce no new matter. Further, the claim 1 system for efficiency comparison is found throughout the original specification, e.g., at paragraphs 27, 62, 64, 68, 121-126, and 170; Figure 7; and, the Examples.

With regard to claim 6, support for Archaeal components can be found throughout the specification, e.g., at paragraphs 58 and 93; Figures 1 and 3; and, in the Examples section.

Applicants submit that no new matter has been added to the application by way of the above claim amendments. Accordingly, entry of the Amendment is respectfully requested.

The Action of May 7, 2008 included: acknowledgement of election, objections to the specification/compliance with the sequence rules, claim objections, and rejections for alleged lack of written description and alleged lack of enablement. Applicants traverse all rejections and objections, to the extent that they may be applied to the amended claims, for the reasons noted herein.

The Election/Restriction Requirement

Pursuant to a restriction requirement made final, Applicants cancel claims 36 to 40, 42 to 50, 52 to 55 and 59 to 64 with entry of this amendment. Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

The Information Disclosure Statement

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the Information Disclosure Statement (Form 1449) submitted on June 21, 2007, February 27, 2007, and September 18, 2006.

Compliance with the Sequence Listing Rules

Applicants note that all required sequences were presented in the Sequence Listing as filed. Applicants have amended the specification to provide SEQ ID NOs where appropriate, as follows.

Paragraphs 0202 and 0203 have been amended to provide SEQ ID NOs for the primers as requested by the Examiner.

Applicants note that where the amino acid sequences of synthetases PhΔAD and PhE444G are presented in Table 1 they are assigned SEQ ID NOs (28 and 30, respectively). Given that the I41 and S268 mutants of PhΔAD refer to variants of the sequence presented as SEQ ID NO:28 and that wild type PhKRS refers to the wild type form of the sequence presented as SEQ ID NO:30, these variants are discussed with respect to the general sequence and need not each be presented as a separate sequence in the Sequence Listing. See, e.g., MPEP 2422.03. For clarity, however, Applicants have amended claims 1, 7, and 8 as noted above to add the SEQ ID NO for the PhΔAD amino acid sequence as requested by the Examiner.

Sequences CUCUAAA and CUUCCUAA in claim 12 have not been assigned sequence identifiers, since they have fewer than ten nucleotides and as such are not subject to the sequence rules (37 CFR 1.821).

Sequence identifiers have been added to the Brief Description of the Drawings for Figures 1, 3, and 5 as requested by the Examiner.

Applicants believe the above amendments bring the application into compliance with the Sequence Rules.

Objections to the Specification

Attorney docket numbers have been replaced in paragraphs 0174 and 0188 with the corresponding application publication number or application serial number, as requested by the Examiner.

The informalities noted by the Examiner have also been corrected. We appreciate the Examiner's careful review of the specification. Paragraphs 0004 and 0061 have been amended to correct the typographical errors noted in the Action. (Paragraphs 0202 and 0203 have also been amended to correct obvious typographical errors.) Paragraphs 0121 and 0124 have been amended to refer to the desired synthetases - support for the amendments can be found, e.g., at paragraphs 0014 and 0015 of the application, as filed. Paragraph 0201 has been amended to remove cited ambiguity, without addition of subject matter.

Objections to the Claims

The Office had objected to the presence of abbreviations in the claims. Applicants note that the cited terms are not so much abbreviations as, e.g., proper names of certain well characterized proteins. However, in order to further clarify the nature of the identified system component, Applicants have expanded the description of the component in the claim. For example, "PhΔAD" is noted as a mutant of *Pyrococcus horikoshii* tRNA synthetase on first introduction in the claims. Applicants respectfully request withdrawal of the objection.

35 U.S.C. §112, First Paragraph.

Claims 1-3, 6-13, 15-19, 21, 22, 36-40, 42-50, 52-55, and 59-64 were rejected under 35 U.S.C. §112, first paragraph, alternately for alleged inadequate written description or alleged lack of enablement. To the extent the rejection is deemed applicable to the amended claims, Applicants traverse.

Applicants note that the same independent claim has been carefully considered and found enabled in granted European patent EP1666604, without amendment. Here, we further clarify the claim to address objections of the U.S. Office.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V. v. Diamond*

Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003). Here, as discussed below, the original written description of the invention is exhaustive and shows the inventors possessed the ability to practice the full scope of the inventions, including any desired specific embodiments.

With regard to the enablement requirement, there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of guidance provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In re Wands, reversed the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement. In *Wands*, the court noted that there was no disagreement as to the facts, but merely a disagreement as to the interpretation of the data and the conclusion to be made from the facts. The Court held that the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406. After considering all the factors related to the enablement issue, the Court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." *Id.*, 8 USPQ2d at 1407. Here, as in Wands (and discussed above), the level of skill in the art is high and considerable guidance is provided to practice the claimed invention. Further, here the scope of the claims is less broad, the rate experimental of success is higher, and more working examples are provided, than in *Wands*.

In the rejections, the Office does not dwell on each *Wands* factor, but lays out a rationale based on 1) variability in the "point of reference" standard translation system for efficiency comparisons, and 2) alleged lack of adequate guidance in teaching the scope of the

claimed systems and cells. The Action appears to acknowledge at least adequate written description and enablement of compositions comprising mutant RSs derived from *Pyrococcus horikoshii* and O-tRNAs derived from a consensus of archaeal lysyl tRNA, that function to incorporate homoglutamine into a protein.

As a preliminary matter, the claims have been amended to further clarify and more precisely define the point of reference standard translation system that was objected to in the Action. Because the standard translation system for comparison focuses on a single, well characterized enabled embodiment (comprising the O-RS of SEQ ID NO.: 28, the OtRNA of SEQ ID NO.: 26 and the unnatural amino acid homoglutamine), Applicants respectfully request withdrawal of section 112 rejections based on the alleged variability of the point of reference for comparing systems in the claims.

The original specification extensively describes generic concepts and methods enabling one of skill to practice of the invention across the scope of the claimed invention. Applicants note that the present specification additionally teaches at least a variety of specific embodiments of working translation system components, including structures important to desired functions.

Breadth of Claims. The claims are not excessively broad. For example, independent claim 1 is specifically limited to translation systems comprising orthogonal lysyl tRNA, homoglutamine, and an orthogonal synthetase that specifically charges the lysyl O-tRNA with homoglutamine. The claimed translation systems are further limited by the requirement that they have a translation efficiency at least 50% of a known standard system. Each of these limitations are extensively described and enabled, as discussed below.

Skill is High. The level of skill is high. The level of skill of practitioners in the field was considered "high" for the *Wands* decision. Obviously, the level of skill in manipulation of biologic systems is much higher now than it was for Wands in 1988. The information that biotechnology practitioners are presumed to be aware of has had over 20 years to develop, and the pace of development during that period has been staggering. A typical postdoctoral researcher or principal investigator can, for example, sequence and provide a detailed analysis of an entire genome, or, e.g., hundreds of cloned RS or OtRNA, in a matter of weeks, whereas in 1988, a week could go by to get one simple sequencing reaction to work,

due to the extensive manual manipulations that had to be performed at the time. If the level of skill in the art was "high" at the time of Wands then it is now positively stratospheric. In any case, any moderately competent molecular biologist, given Applicants' disclosure can certainly perform each and every step required to make the claimed systems of, e.g., lysyl tRNA/RS pairs to charge homoglutamine at a level, e.g., lower than practiced in the present specification.

Predictability in Preparing Desired Embodiments of the Claimed Systems has been Shown to be Good. Employing the methods described in the specification, in light of the extensive supporting scientific references provided, the likelihood that one of skill could practice a desired embodiment of the claimed invention is high. The specification generally outlines steps to produce functioning systems. The specification specifically describes rationales and structural relationships for production of functioning system components and combinations of components. The predictability of success is well demonstrated by the pioneering work of the present inventors, who had a high degree of routine success without the hindsight guidance of the present specification. For example, at paragraph 101, the inventors ventured to pair a *Pyrococcus horikoshii* tRNA synthetase with a theoretical consensus tRNA construct, and it functioned as predicted. At paragraph 196, a "halobacterial tRNA was ... anticipated to be readily charged by PhKRS", and it was. At paragraph 209, the theoretical PhΔAD/AK_{CUA} pair was constructed and it functioned as predicted to suppress an amber mutation in an orthogonal system. At paragraph 212, when investigators attempted to mutate an RS to charge its cognate orthogonal tRNA the with the desired homoglutamine unnatural amino acid, 5 of 15 colonies (33%) screened provided different synthetases functioning in the orthogonal system to incorporate homoglutamine. Applicants note that in the enabled *Wands* claims to screening antibodies, a success rate of only 2.8% was deemed predictable and enabled.

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). From the discussion above, it is clear the amount of guidance required to enable the claims should be minimal,

however, as discussed below, the guidance provided in the present exceptional specification is exhaustive.

Guidance is Extensive. The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004). Here, the technology required to practice the invention is reasonably predictable in the hands of one of skill in the well-developed art. Required experimentation is drastically reduced by the comprehensive guidance provided in the specification.

The specification describes generically how one of skill can practice the invention to acquire any desired translation system embodiment, within the general scope of the claims, to incorporate homoglutamine into a peptide. For example, one of skill can identify an RS/tRNA pair that would be orthogonal in a desired *in vitro* system or host cell. The orthogonal pairs have been shown to predictably work in the host system with some degree of functionality, e.g., in routinely suppressing a stop or frame shift mutation. The functionality can be improved by directed engineering and/or random mutation and screening of RS and/or tRNA orthogonal components. Finally, the orthogonal RS can be further engineered and/or screened to selectively charge the cognate tRNA with homoglutamine, e.g., based on commonly available RS crystallography data for the RS or related RSs. The original specification teaches a variety of methods of preparing the claimed system components and combinations, e.g., in the section entitled "Orthogonal tRNA (O-tRNA)" at paragraphs 68 to 84; the section entitled "Orthogonal aminoacyl-tRNA synthetase (O-RS)" at paragraphs 85 to 92; and, the section entitled "Orthogonal Components for Incorporating Homoglutamine" at paragraphs 120 to 136.

The specification describes structures influencing function for the claimed translation system components and component combinations. This guidance greatly enhances the likelihood of success in designing systems of the claims and minimizes experimentation. For example, important structural/functional guidance providing O-tRNAs of the claims includes:

the tremendous general knowledge in the art concerning the functions of the "cloverleaf" stem and leaf loop structures of tRNAs; the robust orthogonal suppressor (CU(X)XXXAA) tRNA anticodon loop described in paragraph 194; the consensus suppressor strategy discussed in paragraphs 194 et seq.; inspection of proposed sequences for non-canonical base pairs or base mismatches in stem regions in paragraph 198; and, the identification of a key orthogonal discriminator base 73 discussed at paragraph 195. Specific structural/functional guidance is provided with regard to O-RSs of the claims, substantially reducing required experimentation. For example, in Figure 6 and at paragraphs 121 and 212, key active site amino acid residues E41 and Y268 of PhYRS are identified. Analogous residues would be found generically in other archaeal lysine tRNA synthetases. At paragraph 203, truncation after residue S357 is identified as providing better functionality with tRNAs having anticodon mutations.

Working Examples are Abundant. Working examples are provided for methods to provide functioning system components and to combine and enhance desired components to work together in charging homoglutamine. Further, the original specification provides a number of functioning systems, a range of specific working components, and a number of components that could be modified (using the described methods) to provide functioning component combinations, depending on the desires of the technician.

The body of the specification provides working examples of methods to prepare a broad range of working systems of the invention. The Examples section teaches a range of specific embodiments of working method process intermediates, working system components and working system combinations.

System components were readily prepared. As noted above, an archaeal tRNA and RS from another Archaeal genus were selected as a functioning pair at paragraph 196. At paragraph 198 an orthogonal archaeal amber suppressor tRNA was constructed that functioned with PhKRS and PhΔRS. The orthogonal archaeal amber suppressor tRNA ultimately functioned to receive homoglutamine. At paragraph 208 PhΔAD was found to preferentially charges whole halobacterial tRNA. PhΔAD was found to function well in combination with tRNAs suppressing either frame shift or amber mutations, see, e.g., paragraphs 240 and 209. At paragraph 211 multiple orthogonal tRNAs were readily cloned

that function with PhΔAD. At paragraph 212, five different RS clones were identified in one experiment, working with a lysyl O-tRNA to incorporate homoglutamine.

The working examples demonstrate that functioning orthogonal pairs are readily provided in light of the teachings and references described in the original specification. The working examples include at least five examples of, e.g., claim 1 translation systems. The working examples of methods and intermediate system components enable ready preparation of additional working examples, as desired, without undue experimentation.

Quantity of Experimentation is Minimal to Practice the Claimed Invention. As noted above, because the claims are not broad, the skill in the art is high, guidance is extensive, and success predictable, experimentation would be minimal to practice the invention, as claimed. For example, identification of orthogonal pairs is routine. The success rate was high in modification of a given orthogonal pair to specifically charge with homoglutamine. The success rate is would be even greater for future practitioners of the invention, given the lessons provided in the original specification. Given the knowledge provided, it should not be considered undue experimentation to provide a system with at least half the efficiency of a given working embodiment standard system.

CONCLUSION

In view of the foregoing, Applicant(s) believe(s) all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 337-7871 to schedule an interview.